CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

FLUMICLORAC-PENTYL

Chemical Code # 5090, **Tolerance #** 52201
SB 950 # New A.I.

February 1, 2006

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect indicated
Chronic toxicity, dog:	No data gap, no adverse effect indicated
Oncogenicity, rat:	No data gap, no adverse effect indicated
Oncogenicity, mouse:	No data gap, no adverse effect indicated
Reproduction, rat:	No data gap, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect indicated
Teratology, rabbit:	No data gap, no adverse effect indicated
Gene mutation:	No data gap, no adverse effect indicated
Chromosome effects:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect indicated
Neurotoxicity:	No study submitted nor required at this time

Toxicology one-liners are attached.

All record numbers through 219207 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T060201
Revised by T. Moore, 2/1/06

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 52201-0008; 219194; "Combined Chronic Toxicity and Oncogenicity Study of V-23031 by Dietary Administration in Rats"; (H. Adachi; Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1716; 4/10/92); Fifty Crj: CD(SD) rats/sex/group received 0, 100, 1000, 10000, or 20000 ppm of S-23031 Pure (lot no. PYG-88092-M, purity: 94.4%) in the diet for 24 months ((M) 0, 3.5, 35.4, 360.4, 744.9 mg/kg/day, (F) 0, 4.3, 43.6, 443.8, 919.4 mg/kg/day). Fourteen animals/sex/group (except for the 20000 ppm males in which only 12 animals were included) received the same treatment regimen for 12 months ((M) 0, 4.2, 40.3, 415.7, 851.1 mg/kg/day, (F) 0, 5.1, 49.8, 514.3, 1051.6 mg/kg/day). There was no treatment-related effect upon the mean body weights or food consumption of the treated animals. No treatment-related effect was noted in the hematology, urinalysis or ophthalmology examinations. In the clinical chemistry, the mean gamma globulin-1 serum levels for the 20000 ppm animals were greater than those values for the controls at various time points ((M), week 27, (F) weeks 27, 79 and 106, ($p<0.01$)). The serum gamma glutamyl transpeptidase activity was increased for the 20000 ppm males at 79 and 106 weeks ($p<0.01$). In the necropsy examination, the mean relative liver weights of both sexes in groups 10000 and 20000 ppm were greater than those of the controls at 53 weeks ($p<0.05$ or 0.01). The mean absolute and relative liver weights of the 10000 and 20000 ppm males were greater than those values of the controls at 106 weeks ($p<0.01$). Although the mean relative weights of the 100 and 1000 ppm males were also increased at 106 weeks ($p<0.05$), the effect was not considered to be treatment-related. The mean absolute and relative kidney weights of the 10000 and 2000 ppm females were greater than those values for the controls at 53 weeks ($p<0.05$ or 0.01). The mean relative kidney weight for the 20000 ppm males was also greater than that of the control at 53 weeks ($p<0.05$). The effect upon the kidney weights was less evident at 106 weeks with only the mean absolute weight of the 10000 and 20000 ppm males being greater than that of the controls ($p<0.01$). The histopathology examination did not reveal any treatment-related lesions. **Chronic Dietary NOEL:** (M/F) 1000 ppm ((M): 35.4 mg/kg/day, (F) 43.6 mg/kg/day) (based upon the increased liver weights noted for both sexes in the 10000 ppm treatment group); **Oncogenicity was not evident. Study acceptable.** (Moore, 12/6/05)

CHRONIC TOXICITY, RAT

See Combined, rat above.

CHRONIC TOXICITY, DOG

** 52201-0003; 219105; "Chronic Toxicity Study in Dogs of S-23031"; (D.W. Dalgard; Hazleton Washington, Inc., Vienna, VA; Study No. 343-233; 8/26/92); Five beagle dogs/sex/group were dosed orally with 0, 10, 100 or 1000 mg/kg/day of S-23031 technical grade (lot no. PYG-89081-M; purity: 94.6%) in capsules for 52 weeks. No deaths resulted from the treatment. The males in the 1000 mg/kg group demonstrated a lower mean body weight gain over the course of the study (NS). In the hematology evaluation, the activated partial thromboplastin time was increased at various time points for both sexes in the 1000 mg/kg group ($p<0.05$). Among the clinical chemistry parameters which were examined, the serum alkaline phosphatase activity levels for the both sexes in the 1000 mg/kg group were greater than those of the control at various time points during the study ($p<0.05$). The ophthalmological examinations or urinalyses did not reveal any treatment-related effects. The mean relative liver weights of both sexes in the 1000 mg/kg group were greater than those of the control ($p<0.05$). No treatment-related lesions were noted in the histopathological evaluation. **No adverse effect indicated. Dog Chronic Oral Toxicity NOEL:** (M/F) 100 mg/kg/day (based upon the increased relative liver weights of both sexes and lower body weight gain and increased activated partial thromboplastin time for the males in the 1000 mg/kg group). **Study acceptable.** (Moore, 11/16/05)

ONCOGENICITY, RAT

See Combined, rat above.

ONCOGENICITY, MOUSE

** 52201-0004; 219106; "Oncogenicity Study of S-23031 by Dietary Administration in Mice"; (H. Adachi; Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1842; 5/8/92); Fifty-one CD-1 (ICR) mice/sex/group received 0, 300, 3000 or 7000 ppm of S-23031 (lot no. PYG-88092-M, purity: 94.7%) in the diet for 78 weeks ((M) 0, 31.5, 307.9, 731.4 mg/kg/day; (F) 0, 37.8, 368.1, 850.1 mg/kg/day). Another 15 mice/sex/group were dosed for 52 weeks and then euthanized ((M) 0, 32.6, 312.0, 768.0 mg/kg/day, (F) 0, 38.5, 389.3, 899.4 mg/kg/day). There was no treatment-related effect upon the survival of the study animals. The mean body weights and food consumption were not affected by the treatment. In the hematology evaluation, the mean hemoglobin concentrations and hematocrits of the 3000 and 7000 ppm males were less than the control values at 53 weeks ($p<0.01$). At 78 weeks, the mean red blood cell counts, hemoglobin concentrations and hematocrits for these males were less than those of the controls ($p<0.05$ or 0.01). The mean absolute and relative liver weights for the 7000 ppm males were greater than those values for the controls at 53 weeks ($p<0.01$). The mean absolute and relative liver weights for the 3000 and 7000 ppm males were greater than those values for the controls at 78 weeks, when the values were recalculated after removal of data from animals having livers with masses, nodules or cysts ($p<0.01$). The histopathological evaluation of the liver identified the incidence of hepatocellular hypertrophy in the 3000 and 7000 ppm groups (53 weeks: 0: 0/10 vs. 3000: 9/10, 7000: 10/10; 78 weeks: 0: 4/51 vs. 3000: 34/51, 7000: 37/51) ($P<0.01$). There was an increased incidence of metastatic lymphoma/leukemia for the 7000 ppm males in the main study (0: 2/51 vs. 7000: 7/51, NS). However, this incidence was considered to be unrelated to the treatment as 3 of the animals in the high treatment group survived to the termination of the study and did not demonstrate high white blood cell counts and the females did not demonstrate a similar effect. The 7000 ppm males in the main group also had a higher incidence of lung adenomas (0: 2/51 vs. 7000: 7/51). This effect was not demonstrated in the females and was considered to be incidental. **No adverse effect indicated. Mouse Chronic Dietary NOEL:** (M) 300 ppm (31.5 mg/kg/day) (based upon the hematological and hepatic effects noted for the males in the 3000 ppm group), (F) 7000 ppm (850.1 mg/kg/day) (based upon the lack of treatment-related effects at the highest dose level). **No oncogenicity evident. Study acceptable.** (Moore, 11/17/05)

REPRODUCTION, RAT

** 52201-0006; 219113; "A Dietary Two-Generation Reproduction Study of S-23031 in Rats"; (M.D. Nemec; WIL Research Laboratories, Inc., Ashland, OH; Study No. WIL-118008; 5/10/91); Thirty Crl:CD BR rats/sex/group received 0, 200, 10000, or 20000 ppm of S-23031 (lot no. PYG-88092-M; purity, 94.7%) for two generations. The treatment periods for the F0 generation included at least 10 weeks prior to mating, mating and 3 weeks each of gestation and lactation. At that time, 30 F1 weanlings/sex/group were selected as parents and treated for at least 10 weeks prior to mating, mating, and 3 weeks each of gestation and lactation. Clinical signs in both sexes of the 10000 and 20000 ppm groups of both parental generations included brown, tan or yellow staining of the anogenital and urogenital regions in a dose-related manner. The mean body weights of both sexes in the 20000 ppm group and the males in the 10000 ppm group of the F1 generation were less than those of the controls at the end of the premating period ($p<0.05$ or 0.01). There was no apparent effect upon food consumption for animals in either generation. The mean absolute and relative kidney weights of the F0 10000 and 20000 ppm females and of both sexes in the 10000 and 20000 ppm groups in the F1 generation were greater than those values for the control ($p<0.05$ or 0.01). The mean relative kidney weight for the F0 20000 ppm males was also greater than that of the controls ($p<0.01$). The mean relative liver weights of both sexes in the 10000 and 20000 ppm groups of both generations were greater than the control values ($p<0.05$ or 0.01). The mean absolute liver weights of the F0 10000 ppm females, both sexes in the F0 20000 ppm group and the F1 10000 ppm and 20000 ppm males were greater than those values for the controls ($p<0.05$ or 0.01). In the histopathological examination, there was an increased incidence of renal nephropathy in the 10000 and 20000 ppm males of both generations (F0: 0: 4/30 vs. 10000: 13/30, 20000: 13/30; F1: 0: 3/30 vs. 10000: 7/30, 20000: 17/30 ($p<0.05$)). There was an increased incidence of cytoplasmic vacuolation in the liver of the

F1 20000 ppm males (0: 1/30 vs. 20000: 4/30). There were no apparent treatment-related effects on the reproduction parameters of both generations. In the development of the offspring, the mean body weight of the F2 offspring on day 21 of lactation was less than that of the control ($p<0.01$). **No adverse effect indicated.**. **Parental NOEL:** 200 ppm (M: 17 mg/kg/day, F: 19 mg/kg/day) (based upon the incidence of anogenital and urogenital staining in both sexes of both generations, the lower mean body weight of the females in the F1 generation and greater mean absolute and/or relative liver and kidney weights for both sexes in the 10000 ppm treatment group), **Reproductive NOEL:** 20000 ppm (M: 1821 mg/kg/day, F: 1553 mg/kg/day) (based upon lack of reproductive effects on the highest treatment group), **Developmental NOEL:** 10000 ppm (F: 1716 mg/kg/day) (based upon the lower mean body weights of F2 offspring during the lactation period of the 20000 ppm groups). **Study acceptable.** (Moore, 11/9/05)

TERATOLOGY, RAT

** 52201-0005; 219111; "Rat Teratology Study with S-23031"; (J.K. Lemen; Hazleton Laboratories America, Inc., Vienna, VA; Study No. 343-223; 2/21/91); Twenty five mated female Crl:CD BR rats/group were dosed orally by gavage with 0 (aqueous 0.5% methylcellulose), 50, 500 or 1500 mg/kg/day of S-23031 (lot no. PYG 88092M, purity: 94.4%) from day 6 through day 15 of gestation. No deaths resulted from the treatment. There was no apparent treatment-related effect upon the mean body weight gain or food consumption of the treated dams. The treatment did not affect the development of the fetuses. **No adverse effect indicated. Maternal NOEL:** 1500 mg/kg/day (based upon the lack of a treatment-related effect upon the dams in the highest treatment level)
Developmental NOEL: 1500 mg/kg/day (based upon the lack of a treatment-related effect upon the fetuses in the highest treatment level); **Study acceptable.** (Moore, 11/22/05)

Range-finding Teratology Studies

52201-0005; 219110; "Range-Finding Study for Teratology Study in Rats with S-23031"; (S.L. Morseth; Hazleton Laboratories America, Inc., Vienna, VA; Study No. 343-222; 5/22/90); Six mated female Crl:CD BR rats/group were dosed orally by gavage with 0 (vehicle: 0.5% aqueous methyl cellulose), 300, 500, 1000 or 1500 mg/kg/day of S-23031 (lot no. PYG 88092M, purity: 94.4%) from day 6 through day 15 of gestation. Two additional groups of 6 animals/group were dosed with 0 or 1500 mg/kg of the test material because the test material was inadequately mixed at the high dose level for the animals in the main study. There were no maternal treatment effects noted in any of the study groups. There was no treatment-related effect upon evident upon the development of the fetuses. **No adverse effect indicated. NOEL** not assigned due to the cursory nature of the data. **Study supplemental.** (Moore, 11/21/05)

TERATOLOGY, RABBIT

** 52201-0004; 219109; "Rabbit Teratology Study with S-23031" (J.K. Lemen; Hazleton Laboratories America, Inc., Vienna, VA; Study No. 343-221; 2/22/91); Seventeen mated female Hra:(NZW) SPF rabbits/group were dosed orally by gavage with 0 (aqueous methyl cellulose (% not specified)), 100, 200, 400 or 800 mg/kg/day of S-23031 (lot no. PYG 88092M, purity: 94.4%) from day 7 through day 19 of gestation. One female in the control group died on day 16 due to a gavage error. One female in the control group and 4 females in the 800 mg/kg group were found dead on days 19, 13, 17 and 26 (2 dead), respectively. One of the does in the 800 mg/kg group aborted on day 24 prior to death. One other doe in the 800 mg/kg group aborted as well. The 800 mg/kg does demonstrated a mean weight loss during the treatment period. There were no treatment-related effects on the development of the fetuses. **No adverse effect indicated.**
Maternal NOEL: 400 mg/kg/day (based upon maternal mortality and body weight loss noted for the does in the 800 mg/kg treatment group); **Developmental NOEL:** 800 mg/kg/day (based upon the lack of developmental effects in the highest treatment level); **Study acceptable.** (Moore, 11/21/05)

Range-finding Teratology Studies

52201-0004; 219108; "Range-Finding Rabbit Teratology Study with S-23031"; (S.L. Morseth;

Hazleton Laboratories America, Inc., Vienna, VA; Study No. 343-220; 5/24/90); Six mated female Hra:(NZW) SPF rabbits/group were dosed orally by gavage with 0 (vehicle: 0.5% aqueous methyl cellulose), 300, 500, 1000 or 1500 mg/kg/day of S-23031 (lot no. PYG 88092M, purity: 94.4%) from day 7 through day 19 of gestation. One female in the 500 mg/kg group, 3 females in the 1000 mg/kg and 5 females in the 1500 mg/kg group died during the study. There was a dose-related decrease in body weight gain for the 500, 1000 and 1500 mg/kg groups. Food consumption was affected in a dose-related manner for the three higher treatment groups. The incidence of late resorptions per litter was elevated for the 1000 mg/kg group. There was only one litter to evaluate in the 1500 mg/kg group. **No adverse effect indicated. NOEL** not assigned due to the cursory nature of the data. **Study supplemental.** (Moore, 11/18/05)

52201-0004; 219107; "5-Day Oral Toxicity Study in Female Rabbits with S-23031"; (S.L. Morseth; Hazleton Laboratories America, Inc., Vienna, VA; Study No. 343-219; 5/24/90); Five female Hra:(NZW) SPF rabbits/group were dosed orally by gavage with 0 (vehicle: aqueous methyl cellulose (% not reported)), 300, 500, 1000 or 1500 mg/kg/day of S-23031 (lot no. PYG 88092M, purity: 94.4%) for 5 days. No deaths resulted from the treatment. The 1000 and 1500 mg/kg females demonstrated a lower mean body weight gain and food consumption over the course of the study. No treatment-related lesions were evident in the necropsy examination. **No adverse effect indicated. NOEL** not assigned due to cursory nature of data. **Study supplemental.** (Moore, 11/17/05)

GENE MUTATION

** 52201-0009; 219201; "Reverse Mutation Test of S-23031 in *Salmonella typhimurium* and *Escherichia coli*"; (S. Kogiso; Sumitomo Chemical Co., Ltd., Biochemistry and Toxicology Laboratory, Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1677; 8/22/89); *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *E. coli* strain WP2uvrA were treated with S-23031 (lot no. PYG-88092; purity: 94.4%) at concentrations ranging from 100 to 5000 ug/plate with a preincubation of 20 minutes and an incubation with plate incorporation for 65 hours at 37^{o} C under conditions of activation and non-activation. Two trials were performed with duplicate samples for each treatment level. A Kanechlor-400-induced rat liver S9 fraction was used to metabolize the test material. There was no treatment-related increase in the incidence of reverse mutation. **No adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 12/7/05)

CHROMOSOME EFFECTS

**** 52201-0007; 219192, 219193**; "*In Vitro* Chromosomal Aberration Test of S23031 in Chinese Hamster Ovary Cells (CHO-KI)"; (S. Kogiso; Sumitomo Chemical Co., Ltd., Biochemistry and Toxicology Laboratory, Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1875; 11/20/89, amended, 11/10/92); Chinese Hamster Ovary cells (CHO-K1) were incubated with S-23031 (lot no. PYG-88092; purity: 94.4%) at concentrations ranging from 50 to 200 _g/ml (nonactivated) or 100 to 400 _g/ml (activated) at 37^{o} C. The non-activated samples were treated for 18 or 24 hours. The activated samples received 2 hours of treatment and an additional 8 or 16 hours of incubation. In both assays, the cells were incubated the last 2 hours with Colcemid prior to fixation. All of the incubations were performed with duplicate cultures. An Aroclor 1254-induced rat liver S9 fraction was used to metabolize the test material. There was a treatment-related increase in the percentage of cells with chromosomal aberrations under assay conditions of non-activation. **Adverse effect indicated.** The positive controls were functional. **Study acceptable.** (Moore, 12/6/05)

DNA DAMAGE

** 52201-0007; 219191; "Micronucleus Test of S-23031 in ICR Mice"; (M. Hara; Biochemistry and Toxicology Laboratory, Sumitomo Chemical Co., Ltd., Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 2031; 5/25/90); Two studies were perfomed, a time-course study and a dose-response study. In the time course study, fifteen ICR mice/sex were dosed orally by gavage with 5000 mg/kg of S-23031 (lot no. PYG-88092-M; purity: 94.7%). Five animals/sex/time point were euthanized at 24, 48 and 72 hours post-dose. In addition, 5 animals/sex/group were dosed with 10 ml/kg of corn oil (negative control) or 80 mg/kg of cyclophosphamide (positive control) and

euthanized at 24 hours post-dose. In the dose-response study, five mice/sex/group were dosed with 0 (corn oil), 1250, 2500 or 5000 mg/kg of the test material or 80 mg/kg of the cyclophosphamide and euthanized at 24 hours post-dose. Bone marrow samples from the femurs of each animal were examined and the 1000 polychromatic erythrocytes (PCE) per animal were examined for micronuclei. The ratio of PCE's to the total number of erythrocytes (PCEs plus normochromatic erythrocytes) was calculated as well. There was no treatment-related increase in the number of PCE's with a micronucleus. **No adverse effect indicated.** The positive control was functional. **Study acceptable.** (Moore, 12/5/05)

** 52201-0009; 219202; "*In Vitro* Unscheduled DNA Synthesis (UDS) Assay of S-23031 in Rat Hepatocytes"; (S. Kogiso; Sumitomo Chemical Co., Ltd., Biochemistry and Toxicology Laboratory, Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1929; 12/12/89); Primary rat hepatocyte cultures were exposed to S-23031 (lot no. PYG-88092-M, purity: 94.7%.) at concentrations ranging from 1 to 300 μg/ml. There were duplicate cultures per treatment level in two trials. The cells were treated for 18 hours at 37^{o} C. Vehicle control (DMSO, 1%) and positive control (2-acetyl-aminofluorene, 0.05 μg/ml) cultures were included in the assays. There was no treatment-related increase in unscheduled DNA synthesis as ascertained by autoradiography. The positive control was functional. **No adverse effect indicated. Study acceptable.** (Moore, 12/7/05)

NEUROTOXICITY

Study not submitted nor required at this time.

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Studies

52201-0001; 219097, 219098; "Three Month Subacute Toxicity Study of S-23031 by Dietary Administration in Rats"; (Y. Yoshida; Sumitomo Chemical Company, Ltd., Environmental Health Science Laboratory, Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1632; 11/9/90); Twelve Crj:CD (SD) rats/sex/group received 0, 100, 1000, 10000 or 20000 ppm of S-23031 (lot nos. PYG-88092 (purity: 94.4%, brown granule) and PYG-88092-M (purity: 94.7%, brown micronized powder)) for 13 weeks in the diet ((M) 0, 6.6, 67.0, 664, 1359 mg/kg.day; (F) 0, 7.4, 73.8, 726, 1574 mg/kg/day). Another 6 animals/sex/group received the same treatment for 4 weeks. No deaths resulted from the treatment. There was no treatment-related effect on the mean body weights or food and water consumption of the study animals. The ophthalmology, urinalysis, hematology and clinical chemistry data did not reveal any treatment-related effects. The mean absolute and relative liver weights for the 20000 ppm males on weeks 4 and 13 and for the 20000 ppm females on week 13 were greater than the control values ($p<0.01$). The mean relative liver weight for the 10000 ppm males on week 13 was greater than that of the controls as well ($p<0.01$). The mean absolute and relative kidney weights for both sexes in the 20000 ppm group and for the females in the 10000 ppm group were greater than those values of the control on week 13 ($p<0.05$ or $p<0.01$). The mean relative liver weights for the 10000 ppm males was greater than the control value on week 13 as well ($p<0.01$). In the histopathological examination, there was an increased incidence of eosinophilic bodies in the tubules of the kidneys of the males in the 20000 ppm group (0: 1/12 vs. 20000: 4/12). No treatment-related histological lesions were evident for the females. **No adverse effect indicated.** Target organs: liver and kidney; **Subchronic dietary NOEL:** (M/F) 1000 ppm ((M) 67.0 mg/kg/day, (F) 73.8 mg/kg/day) (based upon the increased liver and/or kidney weights noted for the 10000 ppm study animals); **Study acceptable.** (Moore, 10/28/05)

52201-0002; 219099; "13-Week Subchronic Oral Toxicity Study of S-23031 Pure in Rats"; (S. Tamano; Dai-kai Institute of Medical Science, Ichinomiya, Japan; Project No. 8803; 8/7/89); Twelve Crj:CD (SD) rats/sex/group received 0, 100, 1000, 10000 or 30000 ppm of S-23031 Pure (lot no. LN-80206, purity: 99.2%) for 13 weeks ((M) 0, 6.46, 64.9, 659, 2087 mg/kg/day, (F) 0, 6.93, 70.6, 724, 2249 mg/kg/day). No deaths resulted from the treatment. There was no treatment-related effect on the mean body weights or food and water consumption of the study animals. The ophthalmology, hematology and clinical chemistry data did not reveal any

treatment-related effects. In the urinalysis, there was increased level of epithelial cells in the urine of the both sexes in the 10000 and 30000 ppm groups ($p<0.05$). The mean absolute spleen weights of the 1000, 10000 and 30000 ppm females and the mean relative spleen weights of the 10000 and 30000 ppm females were less than that of the controls ($p<0.05$ or 0.01). The mean absolute pituitary gland weights of the 10000 and 30000 ppm males was less than that of the controls ($p<0.05$ or $p<0.01$). The mean absolute thyroid weights of the 10000 and 30000 ppm males and the mean relative thyroid weights of the 30000 ppm males were less than those of the controls ($p<0.05$ or $p<0.01$). The mean relative liver weights of the 30000 ppm males were less than that of the controls ($p<0.01$). No treatment-related lesions were evident in the histopathological examination. **No adverse effect indicated. Rat Subchronic Dietary NOEL:** (M) 10000 ppm (659 mg/kg/day) (based upon increased relative liver and decreased relative thyroid weights in the 30000 ppm males), (F) 1000 ppm (70.6 mg/kg/day) (based upon the decrease relative spleen weight for the 10000 ppm females); **Study acceptable.** (Moore, 10/31/05)

Mouse Subchronic Dietary Toxicity Study

52201-0002; 219100; "Three Month Subacute Toxicity Study of S-23031 by Dietary Administration in Mice"; (H. Yamada; Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, Kasugade-naka, Konhana-ku, Osaka, Japan; Study No. 1650; 11/26/90); Six CD-1 (ICR) mice/sex/group received 0, 1000, 3000 or 10000 ppm of S-23031; lot nos. PYG-88092 (purity: 94.4%) and PYG-88092-M (purity: 94.7%) for 3 months ((M) 0, 125.4, 379.2, 1274 mg/kg/day; (F) 0, 152.4, 457.0, 1435 mg/kg/day). Another 6 mice/sex/group were dosed for 4 weeks and then euthanized. No deaths resulted from the treatment. There was no treatment-related effect upon the mean body weights or food consumption of the study animals. In the hematology evaluation, the mean red blood cell counts, hemoglobin concentrations and hematocrits for the 3000 and 10000 ppm males were less than those values of the controls at 4 weeks ($p<0.05$ or 0.01). At 3 months, the mean hemoglobin concentrations and hematocrits for these males were still less than those of the controls ($p<0.01$). No treatment-related effects were evident in the clinical chemistry parameters which were evaluated. The mean absolute and relative liver weights for the 3000 and 10000 ppm males were greater than those values for the controls at both 4 weeks and 3 months ($p<0.05$ or 0.01). The histopathological evaluation of the liver identified the incidence of hepatocellular hypertrophy in the 3000 and 10000 ppm groups (4 weeks and 3 months: 0: 0/6 vs. 3000: 3/6, 10000: 6/6) with the severity of the effects increasing between 4 weeks and 3 months. An increased incidence of hepatocellular vacuolation was noted after 4 weeks of treatment for both sexes in the 10000 ppm group and for the 3000 and 10000 ppm males at 3 months (4 weeks: (M) 0: 1/6 vs. 10000: 6/6, (F) 0: 1/6 vs. 10000: 6/6; 3 months: (M): 0: 3/6 vs. 3000 and 10000: 6/6). An increased incidence of single cell necrosis was noted in the livers of the 10000 ppm males at 4 months (0: 1/6 vs. 10000: 5/6). This effect was less apparent with the animals in the 3 month cohort (0: 4/6 vs. 10000: 5/6). **No adverse effect indicated. Mouse Subchronic Dietary NOEL:** (M) 1000 ppm (125.4 mg/kg/day) (based upon the hematological and hepatic effects noted for the males in the 3000 ppm group), (F) 3000 ppm (457.0 mg/kg/day) (based upon the hepatocellular vacuolation noted for the 10000 ppm females at 4 weeks). **Study supplemental** (the study did not include all of the parameters recommended in a guideline subchronic toxicity study). (Moore, 11/2/05)

Dog Subchronic Oral Toxicity Study

52201-0003; 219101, 219102; "Three-Month Oral Toxicity Study of S-23031 in Dogs"; (M. Nakano; Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, Kasugade-naka, Konhana-ku, Osaka, Japan; Study No. 1823; 1/30/91); Four beagle dogs/sex/group received orally in a capsule 0, 10, 100 or 1000 mg/kg/day of S-23031 (lot no. PYG-88092-M; purity: 94.7%) for 3 months. No deaths resulted from the treatment. Both sexes in the 1000 mg/kg group exhibited lower body weight gain over the course of the study (NS). Mean food consumption was slightly lower than that of the controls as well (NS). The activated partial thromboplastin time for the 1000 mg/kg females was increased above that of the controls ($p<0.01$). In the renal function test, the % retention of PAH in the males of all of the treatment groups was increased over that of the control value for all of the treatment groups ($p<0.01$). However, the values were within the range of the values observed at other time points during the

study. In the myelocrit, the percentage of lipid layer was less for the 10 and 100 mg/kg females and greater for the 1000 mg/kg females ($p<0.01$). However, there was no apparent dose-response for the effect. No treatment-related effects were evident in the electrocardiogram and clinical chemistry evaluation, the ophthalmology examination, the urinalysis, fecal examination, and liver function test. There was no treatment-related effect upon the mean absolute or relative organ weights. The histopathological examination did not reveal any treatment-related lesions. **No adverse effect indicated. Dog Subchronic Oral Toxicity NOEL:** (M/F) 100 mg/kg/day (based upon the lower mean body weight gain and food consumption demonstrated by both sexes in the 1000 mg/kg group and the greater APTT values for the 1000 mg/kg females). **Study acceptable.** (Moore, 11/4/05)

Rat 21-Day Repeated Dosing Dermal Toxicity Studies

52201-0003; 219103; "21-Day Dermal Toxicity Study in Rats with S-23031"; (M. Osheroff; Hazleton Laboratories America, Inc., Rockville, MD; HLA Study No. 343-229; 8/8/91); The skin of 5 Crl: CD® BR rats/sex/group was treated with 0 (vehicle: corn oil), 100, 300, or 1000 mg/kg/day of S-23031 (lot no. PYG-88092 M, purity: 94.7%) for 6 hours per day, 7 days per week for 3 weeks under an occlusive wrap. No deaths resulted from the treatment. There were no treatment-related clinical signs and the treated animals exhibited body weight gain comparable to that of the controls. There was no treatment-related effect evident in the hematology and clinical chemistry data. The treatment did not affect the mean absolute or relative organ weights. The histopathological examination did not reveal any treatment-related lesions. **No adverse effect indicated**. **Systemic Repeated Dosing Dermal Toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of any treatment related effects at the highest dose tested); **Study acceptable.** (Moore, 11/4/05)

52201-0003; 219104; "21-Day Dermal Toxicity Study in Rats with V-23031 (0.83EC)"; (M.R. Moore; Hazleton Laboratories America, Inc., Rockville, MD; Study No. HWA 2615-100; 10/16/92); The skin of five Crl: CD® BR rats/sex/group was treated with 0 (vehicle: distilled water), 100, 300, or 1000 mg/kg/day of V-23031 (0.83 EC) (batch no. V 803L01; a.i.: 10%) for 6 hours per day, 7 days per week for 3 weeks under an occlusive wrap. No deaths resulted from the treatment. There was no treatment-related effect evident in the hematology and clinical chemistry data. The treatment did not affect the mean absolute or relative organ weights. The histopathological examination revealed a dose-related increase in the signs of dermal irritation for the 300 and 1000 mg/kg treatment groups. **No adverse effect indicated**. **Repeated Dosing Systemic Dermal Toxicity NOEL:** (M/F) 1000 mg/kg/day (based upon the lack of any treatment related effects at the highest dose tested); **Dermal Irritation NOEL:** (M/F) 100 mg/kg/day (based upon the incidence of acanthosis and hyperkeratosis at the treatment site of the 300 mg/kg animals). **Study acceptable.** (Moore, 11/8/05)

METABOLISM STUDIES

Metabolism, Rat

52201-0009; 219206, 219207; "Metabolism of S-23031 in Rats; [tetrahydrophthaloyl-1, 2-^{14}C]S-23031"; (H. Matsunaga; Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 2474; 2/26/93); Five Sprague-Dawley rats/sex were dosed orally by gavage with 1 or 500 mg/kg of [THP-^{14}C]S-23031 (lot no. C-91-032A, specific activity: 109 mCi/mmol, radiochemical purity: >99%) and urine and feces samples were collected for 7 days. A third dosing group of 5 animals/sex was treated daily with 1 mg/kg of S-23031 technical, lot no. LN-80206, purity: 99.2% for 14 days, followed by a 1 mg/kg dose with the radiolabeled compound. Urine and feces samples were likewise collected for 7 days. Dosing via the oral route resulted in a greater percentage of the radiolabel being recovered in the feces than in the urine for both the low and high dose treatment regimens. Males treated once or repeatedly with 1 mg/kg excreted approximately 62 to 64% in the feces and 35% in the urine. Females excreted 50 to 55% in the feces and 42 to 48% in the urine. Treatment with 500 mg/kg resulted in fecal excretion of 68% for the males and 61% for the females with unmetabolized parent compound being the predominant moiety. The residual radiolabel in the animals 7 days after treatment was largely isolated in the kidneys and blood, plasma and/or red blood cells. At the 1 mg/kg treatment level, metabolites were identifiable for 53 to 59% of the administered dose. For

the 500 mg/kg group, the identifiable radiolabeled moieties increased to 60 - 64% of the administered dose. The increase was due to the increased recovery of the unaltered test material. The identifiable metabolites revealed the following metabolic reactions: 1) cleavage of the ester bond, 2) cleavage of the imide linkage, 3) hydroxylation of the cyclohexane moiety or cyclohexane ring of the 3, 4, 5, 6-tetrahydophthalimide moiety and, 4) sulfation of the double bond of the 3, 4, 5, 6-tetrahydophthalimide moiety. No time-course blood collection was performed in an effort to characterize the pharmacokinetic parameters of uptake and elimination of the test material. No biliary excretion study was performed as well. Without either of these analyses, the actual absorption from the gastrointestinal tract is not determinable. **Study supplemental**. (Moore, 12/13/05)

52201-0009; 219203; "Metabolism of S-23031 in Rats"; (N. Isobe; Sumitomo Chemical Co., Ltd., Biochemistry and Toxicology Laboratory, Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 1918; 8/8/90, amended, 12/6/91); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 1 or 500 mg/kg of [Phenyl-^{14}C]S-23031 (lot no. C-88-025, specific activity: 195 mCi/mmol; radiochemical purity: >99%) and urine and feces samples were collected for 7 days. A third dosing group of 5 animals/sex was treated daily with 1 mg/kg of S-23031 (lot no. LN-80206, purity: 99.2%) for 14 days, followed by a 1 mg/kg dose with the radiolabeled compound. Urine and feces samples were likewise collected for 7 days. Dosing via the oral route resulted in a significant percentage of the radiolabel being recovered in the feces. Males treated once or repeatedly with 1 mg/kg excreted approximately 56 to 58% in the feces and 40% in the urine. The females excreted 50 to 53% in the feces and 44 to 49% in the urine. Treatment with 500 mg/kg resulted in fecal excretion of 78% for the males and 57% for the females with unmetabolized parent compound being the predominant moiety. The residual radiolabel in the animals 7 days after treatment was largely isolated in the kidneys and blood, plasma and/or red blood cells. At the 1 mg/kg treatment level, metabolites were identifiable for 63 to 70% of the administered dose. For the 500 mg/kg group, the identifiable radiolabeled moieties increased to 73 to 82% of the administered dose. The increase was due to the increased recovery of the unaltered test material. The identifiable metabolites revealed the following metabolic reactions: 1) cleavage of the ester bonds, 2) cleavage of the imide linkage, 3) hydroxylation of the cyclohexane ring of the 3, 4, 5, 6-tetrahydophthalimide moiety and, 4) sulfation of the double bond of the 3, 4, 5, 6-tetrahydophthalimide moiety. No time-course blood collection was performed in an effort to characterize the pharmacokinetic parameters of uptake and elimination of the test material. No biliary excretion study was performed as well. Without either of these analyses, the actual absorption from the gastrointestinal tract is not determinable. **Study supplemental**. (Moore, 12/9/05)

52201-0009; 219205; "Bile Excretion Study of [Phenyl-^{14}C]S-23031 in Male Rats"; (H. Matsunaga; Environmental Health Science Laboratory, Sumitomo Chemical Co., Ltd., Kasugade-naka, Konohana-ku, Osaka, Japan; Study No. 2661; 2/25/93); Three Sprague-Dawley male rats/group were dosed orally by gavage with either 1 or 500 mg/kg of Phenyl-^{14}C]S-23031 (lot no. C-88-025, specific activity: 195 mCi/mmol; radiochemical purity: >99%) and bile, urine and feces samples were collected for 48 hours post-dose. Eighteen to 19% of the administered dose was recovered in the bile during the 1st 48 hours post-dose at both the low and high dose levels. The urine and bile data indicate that approximately 74 and 49% of the administered dose was absorbed for the low and high treatment levels, respectively. The identifiable metabolites revealed the following metabolic reactions: 1) cleavage of the ester bonds and 2) cleavage of the imide linkage. **Study supplemental**. (Moore, 12/9/05)